Case Report

Neuroinvasive West Nile Virus Disease in an Elderly Patient with Diffuse Large B-Cell Lymphoma Treated with R-CHOP Therapy: A Case Report

Arslan et al. West Nile Virus in Turkey

Barış Arslan¹, Hasan Murat Gündüz², Nurdan Ünlü¹, Gökhan Çavuş³, Dilek Menemenlioğlu⁴

¹Clinic of Anesthesia and Intensive Care, Adana City Training and Research Hospital, Adana, Turkey
²Department of Anesthesia and Intensive Care, Çukurova University, Adana, Turkey
³Department of Neurosurgery, Adana City Training and Research Hospital, Adana, Turkey
⁴Medical Microbiology Specialist, Public Health General Directorate, Microbiology Reference Laboratories and Biological Products Department, National Arboviruses and Viral Zoonoses Laboratory, Ankara, Turkey

Address for Correspondence: Barış Arslan, Clinic of Anesthesia and Intensive Care, Adana City Training and Research Hospital, Adana, Turkey
Phone: +90 553 488 09 69 e-mail: arslanbarbsmed@gmail.com

Received: 25 December 2019
Accepted: 17 June 2019

Cite this article as:

Background: The receptors of salmon calcitonin, located in such areas of brain as periaqueductal gray matter (PAG), are responsible for pain modulation.

Case Report: In the current study, the effects of intracerebroventricular (ICV) injection of sCT on behavioral response to pain and on the levels of monoamines in PAG in a biphasic animal model of pain are explored. Animal experimentation study. 45 male rats in four groups were considered (n=6). sCT was infused into the lateral ventricle of the brain (1.5 nmol, with a volume of 5 μl). After twenty minutes, formalin 2.5% was injected (SC) into the right leg claw and pain behavior was recorded on a numerical basis. At the time of the formalin test, the PAG area was microdialyzed. High-performance liquid chromatography (HPLC) method was used to gauge the levels of monoamines and their metabolites. ICV injections of sCT led to the reduction of pain in the formalin test (p<0.05). Dialysate concentrations of serotonin, dopamine, norepinephrine, HIAA, DOPAC, and HMPG increased in the PAG area in different phases of the formalin pain test (p<0.05).

Conclusion: sCT reduced pain by increasing the concentrations of monoamines and the metabolites derived from them in the PAG area.

Keywords: B-cell lymphoma, flaccid paralysis, rituximab, West Nile virus, West Nile virus neuroinvasive disease

West Nile virus (WNV) is a single-stranded RNA virus, was first isolated from a woman’s blood suffering from fever in Uganda in 1937 (1). Transmission of WNV occurs primarily through bites of infected mosquitoes. In a very small number of cases, WNV has also been transmitted through blood transfusions, organ transplants, breastfeeding, or intrauterine exposure (2). The infection is usually asymptomatic but presents as a mild self-limited febrile illness in 20% of the patients (3). Meningitis, encephalitis and flaccid paralysis or a combination of these occur in less than 1% of the WNV infected patients.

Increasing age, immunosuppression, alcoholism and diabetes mellitus are associated with severe West Nile neuroinvasive disease (WNND) (3). Here, we report the case of WNND in an elderly immunocompromised patient presenting as encephalitis and flaccid paralysis. Written informed consent was obtained from the patient’s family members for publication.

Case
A 60-year-old man carried a diagnosis of diffuse large B-cell lymphoma. He had previously received 3 cycles of rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP); however, the fourth cycle was canceled due to neutropenia. After three weeks, he was admitted to the surgical ward with chief complaints of abdominal pain, vomiting, nausea, and abdominal distention. On the same day, he was diagnosed
with ileus and he immediately underwent surgery. On the 3rd hospital day, he developed a persistent fever and rapidly progressing muscle weakness. The patient was then transferred to the intensive care unit (ICU). Upon physical examination, he was conscious and his pupils were bilaterally reactive to light; however, the deep tendon reflexes were absent in all four of his limbs. The power in his upper limbs was 2/5 and that in his lower limbs was 0/5, but there was no sensory loss. His pulse was 110/min, blood pressure was 130/70 mm Hg, and body temperature was 37.5°C. His oxygen saturation was 92% with oxygen therapy. Subsequently, due to respiratory insufficiency, the patient required intubation and sedation. Mechanical ventilation was started on synchronized intermittent mandatory ventilation mode with a tidal volume of 550 ml, positive end-expiratory pressure of 6 cm H2O, pressure trigger sensitivity of -2 cm H2O, fraction of inspired concentration of oxygen at 0.5, ventilatory rate of 16 breaths/min and pressure support of 15 cm H2O. The tremors were a prominent finding in his upper extremities and they also affected his face and lips (Video 1). Additional information about this patient’s history revealed that he had suffered from mosquito bite-like rash, two weeks before his presentation. On the 5th hospital day, lumbar puncture revealed clear and colorless cerebrospinal fluid (CSF) without white blood cell (WBC), 36 mg/dl of glucose, and 106 mg/dl of protein. His blood test results were as follows: 10.3 x 10³ /ml WBCs, 73 x 10³ /ml platelets, 10.1 g/dl hemoglobin. His cranial computed tomography and magnetic resonance imaging (MRI) showed only atrophic changes and his spinal MRI did not reveal any abnormalities. The routine CSF and blood cultures, acid-fast bacillus testing, herpes simplex virus polymerase chain reaction (PCR) were negative. On the 5th day of admission, serum sample was sent to the National Arboviruses and Viral Zoonoses Reference Laboratory (Ankara, Turkey) for testing for arboviral infections. The WNV real-time reverse transcriptase PCR (rRT-PCR) (Anatolia Geneworks, Istanbul, Turkey) was positive but indirect Immunofluorescence Test (IIFT) (Euroimmun, Luebeck, Germany) results were negative for both IgM and IgG. In order to demonstrate the seroconversion, a second serum sample was sent to the laboratory on 9th day but anti-WNV antibodies were still negative.

He underwent a course of plasmapheresis on the second week of his hospital stay. The plasmapheresis regimen consisted of the removal of -1 plasma volume during each cycle for a total of three cycles every other day basis. After undergoing plasmapheresis, the patient's motor strength recovered from a grade of 0 to 2.5 for his upper extremities and a grade of 0 to 1.5 for his lower extremities. Over the course of the next month, the patient showed partial and progressive improvement especially in the upper extremities through physical therapy. He regained his strength a grade of 3/5 for his upper extremities. A third serum sample was positive for anti-WNV-IgG on day 42.

The patient remained dependent on mechanical ventilation and developed ventilator-associated pneumonia due to multidrug-resistant Acinetobacter baumannii and renal failure requiring continuous venovenous hemodiafiltration. The patient did not improve and succumbed to his illness on day 184 after admission to the hospital.

**Discussion**

The symptoms of WNND include fever, headache, stupor, disorientation, coma, tremors, convulsions, muscle weakness, vision loss, numbness, and paralysis (2,3,4). Sejvar (4) et al. reported the most common neurological finding was tremors at a rate of 94%. Likewise, Tilley (5) et al. reported that tremors as the most predictive neurological feature of WNV infection. Previously, there have been immunohistochemical and neuroimaging studies suggesting that viral encephalitis-induced tremors and parkinsonism are due to abnormal changes in the basal ganglia, thalamus, and substantia nigra (3, 6). The patient reported here presented with nausea and vomiting upon admission but later exhibited fever, muscle weakness, and prominent tremors. The patient's tremor with a frequency of 4–5 Hz was prominent in the upper extremity and became apparent when he tried to move his hand through the verbal command (Video 1). Unlike myoclonus, it was rhythmic and there was no jerk. It was reported before that tremor associated with WNND involve mostly the upper extremities and are usually intentional or postural (4).

The differential diagnosis for acute flaccid paralysis includes, but is not limited to WNND paralysis, Guillain-Barré syndrome, Lyme disease, heavy metal toxicity, botulism, myasthenia gravis, spinal cord compression, and poliomylitis (7). Our initial diagnosis was WNND due to the patient’s rash history, known WNV circulation in the geographical area, and prominent tremors. The laboratory diagnostic criteria for WNV defined by the US Centers for Disease Control and Prevention include: (i) isolation of the virus, specific viral antigens, or nucleic acids from the blood, tissues, CSF or other body fluids; and (ii) detection of virus-specific IgM and/or IgG antibodies in serum or CSF. (2). Positive PCR test denotes definitive diagnosis but the viremia is very short and usually resolves by the time the symptoms begin unless the patient is immunosuppressed. Our patient was diagnosed by rRT-PCR on the 5th day of onset of the symptoms which is indicative of a prolonged viremia. As the anti-WNV IgG was found to be positive on the 42nd day, the absence of anti-WNV IgM on the 9th day and the 42nd days may be related to the patient’s immunocompromised status, performed plasmapheresis, or both. Thus, in patients with immunocompromised status and prolonged viremia, detection of WNV RNA in serum would be a more informative and reasonable diagnostic criterium compared to serological detection of WNV-specific antibodies.
Rituximab causes B-cell death by targeting surface protein CD20. Recovery of B-cells begins 6–9 months after the completion of therapy, and generally takes at least 12 months to resume normal levels. B cell depletion can be expected to result in reduced to absent humoral responses to new antigens. Blunted humoral response from rituximab may be accompanied by an increase in neurotropic and opportunistic virus infections. Some fatal viral infections have also been reported after rituximab treatment, such as cytomegalovirus, varicella-zoster virus, hepatitis B virus, enterovirus, and WNND (8, 9). Goates (8) et al. reported that rituximab not only predisposes patients to more severe WNND infection but also results in negative serologic tests leading to delayed diagnosis. Respiratory failure requiring long-term mechanical ventilation support and subsequent tracheostomy have been described with WNND. A high percentage of affected patients need intubation, because of severely reduced level of consciousness, bulbar weakness, diaphragmatic, and, intercostal muscle paralysis (4, 10). According to a retrospective study of 32 patients, respiratory complications were the leading cause of death in WNND presenting with flaccid paralysis (10). Also, the authors reported that successful extubation occurred after prolonged weaning periods (mean duration of intubation 66 days) and often, multiple attempts of extubation and reintubation. In patients with prolonged mechanical ventilation and ICU stay, complications include ventilator-associated pneumonia, aspiration, atelectasis, thromboembolic disease, contractures, and decubitus ulcers. There is no specific treatment for WNND, and patients are managed with supportive care. Although different therapeutic approaches have been suggested, including plasmapheresis, intravenous immunoglobulin, and ribavirin, there is no evidence to support them. Our patient underwent plasmapheresis due to its accessibility at our center, but due to his poor recovery, it remains unclear whether his outcome was affected by this intervention.

Acknowledgements: The authors thank Prof. Dr. Koray Ergunay (Hacettepe University, Ankara, Turkey) for his many helpful comments.

Video 1. The patient with new-onset tremors. Tremors are a very common symptom of West Nile neurological disease. The observed tremors characterized in the patient as upper extremity intention tremors with asymmetrical presentations. In addition to new onset tremors, rapidly progressive muscle weakness and low-grade fever accompanied the symptoms of the patient. This video was recorded on the 10th day in his ICU follow-up.

REFERENCES